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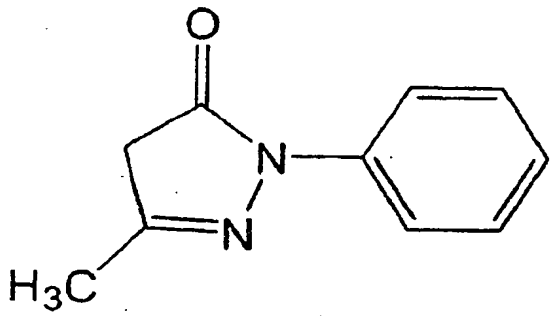
(54) PERCUTANEOUS ABSORPTION PREPARATIONS CONTAINING 3-METHYL-1-PHENYL-2-PYRAZOLIN-5-ONE

(57) The present invention relates to a percutaneous absorption preparation (which may also be in the form of an adhesive preparation) containing, as an active ingredient, 0.1 to 30 percent by mass of 3-methyl-1-phenyl-2-pyrazolin-5-one represented by the following formula:



or a medically acceptable salt thereof in an appropriate base such as an aqueous base or a rubber base. This preparation (or adhesive preparation) is an excellent percutaneous absorption preparation (or percutaneous absorption adhesive preparation) which has good percutaneous absorbability of the active ingredient and causes little skin irritation.

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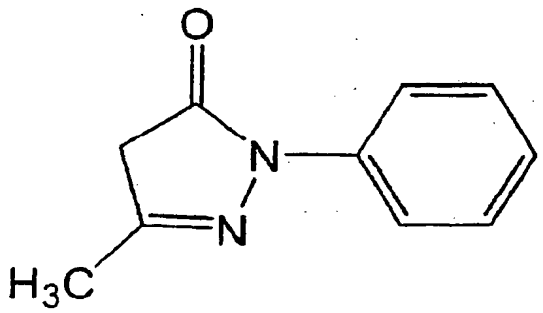
rectally and thus have the drawbacks described above in clinical practice.

DISCLOSURE OF THE INVENTION

[0008] In view of the current situation, the inventors have achieved an invention of a percutaneous absorption preparation containing 3-methyl-1-phenyl-2-pyrazolin-5-one which has a medicinal effect equal to, or greater than, the medicinal effect of 3-methyl-1-phenyl-2-pyrazolin-5-one when used as an injectable solution, and which solves the problems of the related art by employing a form of the percutaneous absorption preparation (also including a form of percutaneous absorption adhesive preparation) as a form of preparation instead of an injectable solution, as a result of intensive study of other methods of administration, aside from the foregoing method of administration, for 3-methyl-1-phenyl-2-pyrazolin-5-one.

[0009] A percutaneous absorption preparation containing 3-methyl-1-phenyl-2-pyrazolin-5-one according to the present invention is characterised in that it contains, as an active ingredient, 0.1 to 30 percent by mass of 3-methyl-1-phenyl-2-pyrazolin-5-one represented by the following formula:



or a medically acceptable salt thereof in a base (hereinafter referred to as i).

[0010] The following percutaneous absorption preparations according to the present invention are preferable.

ii) The percutaneous absorption preparation according to i in which the base is an aqueous base.

iii) The percutaneous absorption preparation according to i in which the aqueous base contains, based on a total amount of the aqueous base, 1 to 20 percent by mass of a water-soluble polymer, 0.01 to 20 percent by mass of a cross-linking agent, 10 to 80 percent by mass of polyhydric alcohol, and 1 to 80 percent by mass of water.

iv) The percutaneous absorption preparation according to i in which the base is a rubber base.

v) The percutaneous absorption preparation according to iv in which the rubber base contains, based on the total amount of the rubber base, 10 to 50 percent by mass of a rubber polymer, 10 to 50 percent by mass of a plasticizer, and 5 to 50 percent by mass of a tackifier.

[0011] This preparation can also be used in the form of an adhesive preparation.

[0012] A percutaneous absorption adhesive preparation containing 3-methyl-1-phenyl-2-pyrazolin-5-one according to the present invention is characterised in that a support medium, a base layer formed of a base containing, as an active ingredient, 0.1 to 30 percent by mass of 3-methyl-1-phenyl-2-pyrazolin-5-one represented by the following formula:

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suitable base.

[0018] The preparation may be in various suitable forms, for example, a solution, a slurry, an ointment, a paste, rubber, or the like, and can be manufactured as it is or in a more suitable form.

[0019] If the preparation is used in the form of an adhesive preparation, it can be applied to the skin in that form which makes it convenient and easy to use. The adhesive preparation may also be in various adhesive preparation forms such as, for example, an adhesive skin patch, a plaster agent, a tape agent, or the like, depending on the use.

[0020] The adhesive preparation can be manufactured by, for example, adding a predetermined amount of 3-methyl-1-phenyl-2-pyrazolin-5-one in a form suitable for coating (such as ointment form) to a suitable base (such as an aqueous base or a rubber base), applying this at a predetermined thickness to a suitable support medium, covering it from above with a predetermined liner, and cutting it to the desired size. Depending on the manufacturing method, the adhesive preparation may also be formed by, for example, first coating a liner with a base containing 3-methyl-1-phenyl-2-pyrazolin-5-one to form a base layer, covering this from above with a support medium, and then transferring the base layer onto the support medium.

[0021] As the aqueous base or the rubber base, an aqueous base made of a mixture of the following components, for example, can be used.

I. Aqueous base

Component 1) : water-soluble polymer
Component 2) : cross-linking agent
Component 3) : polyhydric alcohol

II. Rubber base

Component 4) : rubber polymer
Component 5) : plasticizer
Component 6) : tackifier

[0022] The components 1) to 6) will be hereinafter be described.

[0023] Examples of the water-soluble polymer of component 1) include polyacrylic acid, polyacrylate, polyacrylic acid moiety neutralizer, polyacrylamide, polyethylene imine, polyvinyl alcohol, polyvinylpyrrolidone, carboxy vinyl polymer, methylcellulose, carboxymethylcellulose, carboxymethylcellulose sodium, hydroxyethylcellulose, starch acrylate, ethyl vinyl acetate, gelatin, starch, Eudragid, alginic acid, sodium alginate, tragacanth, and the like. Only one type of water-soluble polymer may be used or two or more types of water-soluble polymers may be suitably mixed together at a predetermined ratio and used. The compound content of the water-soluble polymer is 1 to 20 percent by mass, and preferably 3 to 6 percent by mass, based on the total amount of the water-soluble base.

[0024] As the cross-linking agent of component 2), for example, salts can be used which produce bivalent or trivalent metal ions when dissolved in water or the like. Examples of the cross-linking agent include hydroxides such as aluminum hydroxide and magnesium aluminum hydroxide, or inorganic acid or organic acid salts such as aluminum chloride, aluminum sulfate, dihydroxyaluminum aminoacetate, kaolin, aluminum stearate, magnesium hydroxide, magnesium chloride, and magnesium sulfate, or an aluminate such as sodium aluminate, inorganic aluminum complex salt and organic aluminum chelate compound, synthetic hydrotalcite, magnesium aluminometasilicate, magnesium aluminosilicate, aluminum nitrate, aluminum sulfate, EDTA-aluminum, aluminum allantoinate, aluminum acetate, aluminum glycinal and the like. Only one type of cross-linking agent may be used or two or more types of cross-linking agents may be suitably mixed together at a predetermined ratio and used. The compound content of the cross-linking agent is 0.01 to 20 percent by mass, and more preferably 0.1 to 10 percent by mass, based on the total amount of the water-soluble base.

[0025] The salts that produce bivalent or trivalent metal ions and which serve as the cross-linking agent may be readily soluble in water or may be very insoluble in water. When an aluminum compound that is very insoluble in water is used as the cross-linking agent, a reaction speed adjuster can be added to the reaction system in order to facilitate gelatinization. In particular, the addition of acid makes it possible to increase the reaction speed of the gelatinization. The gelatinization reaction speeds up remarkably by adding an organic acid that includes a hydroxyl group or a salt thereof, in particular, as the acid. Examples of the reaction speed adjuster include organic bases, organic acid salts, and organic acids having a chelate forming ability or coordinating property with respect to metal ions, such as citric acid, lactic acid, tartaric acid, gluconic acid, glycolic acid, malic acid, fumaric acid, meta sulfonic acid, maleic acid, acetic acid, EDTA di sodium, urea, triethylamine, ammonia, and inorganic acids such as hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid and hydrobromic acid.

[0026] Examples of the polyhydric alcohol of component 3) include ethylene glycol, propylene glycol, trimethylene

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dants may be suitably mixed together at a predetermined ratio and used. The compound content of the antioxidant is 0.005 to 20 percent by mass, and preferably 0.1 to 5 percent by mass, based on the total amount of the base.

[0036] The percutaneous absorption accelerator is not particularly limited as long as it is one which is normally used in percutaneous absorption preparations. Examples of the percutaneous absorption accelerator include alcohol, fatty acid, fatty ester, fatty ether, lactic acid ester, acetic ester, terpene compound, pyrrolidone derivative, organic acid, organic acid ester, essential oil, hydrocarbon, azone or a derivative thereof, and the like. More specifically, the percutaneous absorption accelerator is ethanol, oleyl alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol, crotamiton, cyclodextrin, calcium thioglycollate, N-methyl-2-pyrrolidone, ethyl lactate, cetyl lactate, lactic acid, urea, 1-menthol, mentha oil, d-limonene, d1-camphor, or the like. Only one type of percutaneous absorption accelerator may be used or two or more types of percutaneous absorption accelerators may be suitably mixed together at a predetermined ratio and used. The compound content of the percutaneous absorption accelerator is 0.1 to 20 percent by mass, and preferably 0.1 to 5 percent by mass, based on the total amount of the base.

[0037] Examples of the dissolving agent include n-methyl-2-pyrrolidone, crotamiton, macrogol, isopropanol, mentha oil, propylene glycol, butylene glycol, oleyl alcohol, isopropyl myristate, and the like. n-methyl-2-pyrrolidone and crotamiton are particularly effective as dissolving agents due to the high solubility of 3-methyl-1-phenyl-2-pyrazolin-5-one.

(Examples)

[0038] Examples of the present invention will hereinafter be described.

Example 1

[0039] Liquid A was adjusted by mixing 5 parts sodium polyacrylate, 6 parts starch acrylate, 12 parts talc, and 29.1 parts concentrated glycerin. Liquid B was adjusted by dissolving 2.3 parts tartaric acid in 30 parts water. Liquid C was adjusted by dissolving 3 parts 3-methyl-1-phenyl-2-pyrazolin-5-one in 8 parts n-methyl-2-pyrrolidone and 2 parts crotamiton. Liquid B and liquid C were added to liquid A. Also, 2.5 parts methyl acrylate/acrylic acid 2-ethylhexyl copolymer resin emulsion and 0.1 parts aluminum hydroxide gel were added and mixed evenly. A base layer was then formed by spreading this mixture (this preparation) at a predetermined thickness on a polyester non-woven fabric (support medium) of predetermined dimensions (length dimensions x width dimensions x thickness; the same applies hereafter). This base layer was then covered with a polyethylene film (liner) of predetermined dimensions. This was then cut into predetermined dimensions to obtain a percutaneous absorption adhesive preparation containing 3-methyl-1-phenyl-2-pyrazolin-5-one of Example 1.

Example 2

[0040] 20 parts polybutene, 10 parts polyisobutylene, 25 parts styrene-isobutylene-styrene block copolymer, 0.5 parts di-butylhydroxytoluene, 14.5 parts liquid paraffin, 10 parts water absorbing-polymer [starch acrylate 1000 (proprietary name: Sunwet IM 1000)], 17 parts adhesive (proprietary name: Alcon P-100), and 3 parts 3-methyl-1-phenyl-2-pyrazolin-5-one were dissolved in 60 parts isohexane. Then, a base layer was formed by spreading this solution (the preparation) at a predetermined thickness on a polyvinyl chloride sheet (support member) of predetermined dimensions. This was then dried and the solvent removed, after which the base layer was covered with a polyester film (liner). This was then cut into predetermined dimensions to obtain a percutaneous absorption adhesive preparation containing 3-methyl-1-phenyl-2-pyrazolin-5-one of Example 2.

Example 3

[0041] Liquid A was adjusted by mixing, at 140 degrees Celsius, 20 parts polybutene, 10 parts polyisobutylene, 19.5 parts liquid paraffin, 25 parts styrene-isobutylene-styrene block copolymer, 0.5 parts di-butylhydroxytoluene, and 17 parts adhesive (proprietary name: Alcon P-100). Liquid B was adjusted by evenly mixing 3 parts 3-methyl-1-phenyl-2-pyrazolin-5-one into 5 parts propylene glycol. After heating liquid A from room temperature to 120 degrees Celsius, liquid B was then added to, and mixed with, liquid A. A base layer was then formed by spreading this mixture (this preparation) at a predetermined thickness on a polyester non-woven fabric of predetermined dimensions. This base layer was then covered with a polyethylene film (liner) of predetermined dimensions. After being cooled to room temperature, this was then cut into predetermined dimensions to obtain a percutaneous absorption adhesive preparation containing 3-methyl-1-phenyl-2-pyrazolin-5-one of

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section of damaged skin. One hour, 24 hours, and 48 hours after the adhesive preparations were removed, erythema, edema, and scab-formation in the sections was determined according to the criterion of the Draize method. From the results, a skin irritation index (PII) was calculated and evaluated following the evaluation classifications.

[0046] Also, as a control, evaluations were also conducted by a test method similar to the method described above for an adhesive preparation (Control 1) which was adjusted by coating 0.25g of an ointment containing 5 percent by mass of sodium lauryl sulfate and 95 percent by mass of white petrolatum onto a non-woven fabric, and an adhesive preparation (Control 2) which was adjusted by using a preparation of the composition of Example 1 excluding the agent (3-methyl-1-phenyl-2-pyrazolin-5-one).

2) Result

[0047] The results are shown in Table 2 below.

Table 2:

Rabbit primary skin irradiation test		
Adhesive Preparation	Skin Irritation Index (P.I.I.)	Safety Classification
Example 1	0.06	Weak Irritant
Example 2	0.10	Weak Irritant
Example 3	0.10	Weak Irritant
Control 1	6.80	Srtrong Irritant
Control 2	0.06	Weak Irritant

[0048] The adhesive preparation of Examples 1, 2, and 3 is in the range of a weak irritant according to the criterion of the Draize method, just like the adhesive preparation of comparison 2 which does not contain the agent (3-methyl-1-phenyl-2-pyrazolin-5-one). Therefore, it is evident that this adhesive preparation is a percutaneous absorption preparation which causes extremely little skin irritation.

INDUSTRIAL APPLICABILITY

[0049] The percutaneous absorption preparation according to the present invention causes little skin irritation, and, by applying it to the skin of an individual in the form of a percutaneous absorption adhesive preparation, for example, the agent (3-methyl-1-phenyl-2-pyrazolin-5-one), which is an effective ingredient against cerebral dysfunction, can be maintained at an effective concentration over an extended period of time, and can be easily administered by an individual.

[0050] The method of use (starting and stopping administration of the agent) of the preparation or the adhesive preparation is easy, and during use, the agent is gradually absorbed through the skin. As a result, the agent is able to be effective over a long period of time without causing a temporary increase in the concentration of the agent in the blood.

[0051] Further, the preparation or adhesive preparation does not cause the patient pain or restrict the patient for a certain period of time during use as does the conventional injectable solution (intravenous drip infusion).

[0052] Accordingly, the preparation or adhesive preparation is useful for protecting brain functions in humans and improving and preventing cerebral dysfunction with respect to overall cerebral dysfunction including cerebral infarction and subarachnoid hemorrhage and the like, as well as treating and preventing disorders such as arteriosclerosis, hepatic damage, renal damage, diabetes, and gastrointestinal mucous membrane damage.

Claims

1. A percutaneous absorption preparation containing 3-methyl-1-phenyl-2-pyrazolin-5-one, **characterised in that** it contains, as an active ingredient, 0.1 to 30 percent by mass of 3-methyl-1-phenyl-2-pyrazolin-5-one represented by the following formula:

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10. The percutaneous absorption adhesive preparation according to claim 9, **characterised in that** the rubber base contains, based on the total amount of the rubber base, 10 to 50 percent by mass of a rubber polymer, 10 to 50 percent by mass of a plasticizer, and 5 to 50 percent by mass of a tackifier.

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INTERNATIONAL SEARCH REPORT

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PCT/JP02/11518

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61K31/4152, 47/10, 47/30, 9/70, A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61K31/4152, 47/10, 47/30, 9/70, A61P9/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), CAOLD(STN), REGISTRY(STN), WPI/L(DIALOG)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	JP 10-279480 A (Mitsubishi Chemical Corp.), 20 October, 1998 (20.10.98), Claims; Par. Nos. [0012], [0014] (Family: none)	1 2-10
Y	WO 02/00260 A1 (Mitsubishi-Tokyo Pharmaceuticals, Inc.), 03 January, 2002 (03.01.02), Claim 4 (Family: none)	1-10
Y	JP 10-265373 A (Lion Corp.), 06 October, 1998 (06.10.98), Par. No. [0003] (Family: none)	2-3,6-8

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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(54) EXTERNAL PREPARATION CONTAINING TRANILAST AND PROCESS FOR PRODUCING THE SAME

(57) An external preparation containing tranilast which is excellent in the release of the active ingredient contained therein, achieves a high percutaneous absorption, fully ensures the effective drug concentration in the skin tissue and little irritates the skin. This preparation is composed of an aqueous base containing as the active ingredient tranilast, its salt or a mixture thereof. The aqueous base contains a solubilizer for tranilast, a dispersant, an absorption aid, an adhesive and/or a shape retenting agent, and water. The active ingredient has been solubilized by the above-mentioned solubilizer and dispersed in the aqueous base by the above-mentioned dispersant.

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mal absorbability of the active ingredient in the preparation, sufficiently keeps a drug concentration effective in the skin tissues, and shows little skin irritation.

[0010] The earlier report (Toyomi Waseda, The Japanese Journal of Dermatology, 99 (11), 1159 (1989)) describes that the effective concentration of tranilast in the skin tissue for treatment of keloid patients is about 8 to 10 μ g/g when it is orally administered in a dose of 300 mg/day in three divided doses for three days. Another earlier report (Yasuo Goto et al., Kiso to Rinsho (The Clinical Report), 25(15), 69 (1991)) discloses that in the experiment using rat carrageenan-induced granulation tissue model a dose-dependent inhibitory effect was observed when tranilast was orally administered in a dose of 50, 100, and 200 mg/kg for consecutive 14 days and the drug concentration in the skin tissue one hour after the final administration was 4.2± 0.4, 10.3 ± 0.9, and 23.17± 1.7 μ g/g, respectively. Consequently, the tranilast concentration in the skin tissue after its application to the skin should desirably be comparable to or higher than the values as described above.

[0011] Keloid, hypertrophic scar, and allergic dermatitis are diseases giving some appearance on the skin surface that is not only apparently ugly but also sometimes accompanied by strong itchiness or pain as subjective symptoms. Accordingly, it is preferable that preparations for external application to be directly applied to the diseased part should not produce irritation by contact and the base in the preparation does not cause skin irritation. Particularly, patches are preferably elastic and do not have undue strong adhesiveness so that little resistance occur when they are detached. In this connection, a cataplasm containing water or a soft type of plasters is desired.

[0012] The present invention provides a preparation for external application and a method of producing it to achieve the above object, which preparation contains an aqueous base comprising tranilast, its salt, or a mixture thereof as an active ingredient, in which the aqueous base comprises a dissolution medium, a dispersant, an absorption aid, an adhesive, and/or a form-keeping agent, and water, the active ingredient is dissolved in the dissolution medium, and dispersed in the aqueous base by means of the dispersant. The present invention provides such a preparation for external application comprising tranilast and a patch for external application which comprises a support having the preparation for external application coated thereon.

[0013] Further, the present invention relates to a method of producing a preparation for external application containing tranilast, which comprises dissolving an active ingredient selected from tranilast, its salt, or a mixture thereof in a dissolution medium, adding thereto a dispersant, and mixing the solution with an aqueous base comprising an absorption aid, an adhesive, and/or a form-keeping agent, and water, and to a method of producing a patch for external application which comprises coating the above preparation for external application on a support.

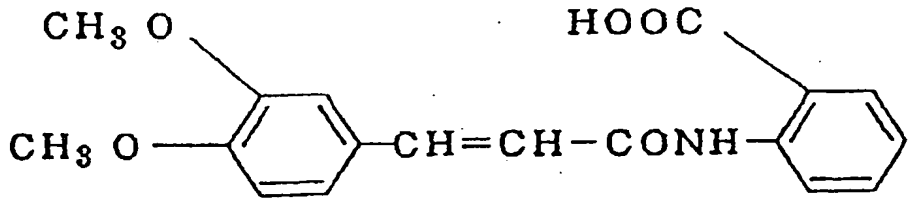
BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

Fig. 1 shows a permeation/diffusion cell used in the test for skin permeation rate of the drug in the preparation of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0015] Tranilast, which is the active ingredient of the preparation for external application of the present invention, is N-(3,4-dimethoxycinnamoyl)-anthranilic acid represented by the following formula or salt thereof:



The content of tranilast in the preparation is preferably 0.05 to 5 wt%. If the content of the active ingredient is too low, its pharmacological effect is insufficient. If it is too high, it does not show additional merit and, thus, is economically disadvantageous.

[0016] In the preparation for external application of the present invention, the dissolution medium to solve tranilast therein is selected from oily substances including fatty acids and derivatives thereof, animal and vegetable oils and fats, terpene compounds, alcohols, crotamiton, N-methyl-2-pyrrolidone, and triethanolamine.

[0017] The fatty acids and derivatives thereof that can be used as the dissolution medium are monocarboxylic acids

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[0029] Examples of fat-soluble polymers that can be used as the adhesive and/or the form-keeping agent include natural rubber, isoprene rubber, polyisobutyrene rubber, styrene-butadiene rubber, styrene-isoprene-styrene block copolymer, styrene-butadiene-styrene block copolymer, silicone, rosin, polybutene, lanolin, petrolatum, plastibase, beeswax, and solid paraffin.

[0030] Polyhydric alcohols that can be used as the adhesive and/or the form-keeping agent include glycerol, polyethylene glycol, ethylene glycol, and D-sorbitol. These can be used alone or in combination of two or more thereof. The total amount to be added is preferably 5 to 40 wt%.

[0031] Using the above-described adhesive and/or form-keeping agent, it is possible to provide the tranilast-containing patch for external application that can keep adhesiveness, its form, and flexibility for a long time, with causing little skin irritation.

[0032] Further, if desired, it is possible to use a nonionic surface active agent or an inonic surface active agent, the other additives for medicines, for example, polyacrylic acid metal salt, bentonite, titanium oxide, and the like, in a necessary amount.

[0033] According to the present invention, the thus-prepared preparation for external application containing tranilast is spread on the support fabric such as flannel, nonwoven fabric, or the like and a film for peeling such as polyethylene, polypropylene, polyester, or the like an the exposed surface of the opposite side of the support fabric. The resulting products can be brought to market as a preparation for external application.

[0034] It is also possible to use the preparation for external application of the present invention as ointment or cream to be directly applied on the diseased part as it is without spreading on the support.

[0035] In the preparation for external application containing tranilast according to the present invention, tranilast, which is sparingly soluble in water, is dissolved in the dissolution medium and dispersed in the aqueous base with being retained by the dispersion medium. Thus, tranilast is uniformly dispersed in the aqueous base. Because of this, the active ingredient is easily released to provide high skin absorbability, its effective concentration in the skin tissue after its application is sufficiently maintained with little skin irritation.

Description of Preferred Embodiment

[0036] The following Examples will demonstrate the present invention in more detail, but are not construed to limit the scope of the present invention.

EXAMPLE 1

[0037] Three g of tranilast was dissolved in a mixed solution of 20 g of crotamiton and 10 g of ethanol by gradually heating to 60 to 70 C. After adding 7 g of white carbon thereto, the mixture was thoroughly mixed and ethanol was removed under reduced pressure. Then, 5 g of 1-menthol and 2.5 g of titanium oxide were added thereto and the mixture was mixed to prepare a tranilast solution. Separately, 25 g of tartaric acid was dissolved in 552 ml of water followed by adding 50 g of sodium polyacrylate, 60 g of polyacrylate starch, and 250 g of glycerol. The resulting mixture was mixed well to prepare an aqueous base mixture.

[0038] The tranilast solution, the aqueous base mixture, 0.5 g of dry aluminum hydroxide gel, and 25 g of methyl acrylate/2-ethylhexyl acrylate copolymer resin emulsion were uniformly kneaded to obtain 0.3% tranilast-containing preparation for external application. The pH of the preparation was 5.2.

EXAMPLE 2

[0039] Three g of tranilast was dissolved in a mixed solution of 20 g of crotamiton and 25 g of N-methyl-2-pyrrolidone. After adding 7 g of white carbon thereto and mixing the solution well, ethanol was removed under reduced pressure. Then, 5 g of 1-menthol and 2.5 g of titanium oxide were added and mixed to prepare a tranilast solution. Separately, 25 g of tartaric acid in 527 ml of water was mixed well with 50 g of sodium polyacrylate, 60 g of starch acrylate, and 250 g of glycerol to prepare an aqueous base mixture.

[0040] The tranilast solution, the aqueous base mixture, 0.5 g of dry aluminum hydroxide gel, and 25 g of methyl acrylate-2-ethylhexyl acrylate copolymer resin emulsion were kneaded uniformly to obtain 0.3% tranilast preparation for external application. The pH of the preparation was 5.2.

EXAMPLE 3

[0041] In the same composition containing tranilast and the base for external application as described in Example 1, 50 g of butanediol was added to the aqueous base mixture and glycerol was used in an amount of 200 g in place of 250 g to obtain 5% butanediol-containing tranilast preparation for external application.

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Table 1

Influences of pH on transdermal absorption of the preparation for external application						
pH of Base	Amount penetrated (μ g/cm^2) n=3					Penetration rate*1
	1 hr	3hr	5 hr	7 hr	24 hr	(5 to 24 hr)
4.3	0.00	0.02	0.15	0.40	4.21	0.22 ± 0.02
5.4	0.00	0.03	0.10	0.40	3.79	0.20 ± 0.03
6.3	0.00	0.00	0.12	0.35	2.93	0.15 ± 0.03
7.4	0.00	0.00	0.04	0.11	0.17	0.06 ± 0.02

*1:μ g/cm^2/hr S.E.

TEST EXAMPLE 2

[0048] In the same manner as in Examples 3 and 4, the preparations were prepared so as to make each of the amount of the absorption aid, propylene glycol and butanediol, 2%, 5%, and and 10% and make the amount of N-methyl-2- pyrrolidone 2.5%. The resulting preparations were respectively spread on the support to give patches. Using the resulting patches, skin absorbability of the skin absorption aids, that is, propylene glycol, butanediol, and N-methyl-2-pyrrolidone, was evaluated by measuring the penetration rate of tranilast and the amount of tranilast accumulated in the skin. The results are shown in Table 2. The skin penetration rate was determined in accordance with the method as described in Test Example 1. The drug concentration in the skin was determined as described below.

[0049] Abdominal body hair of Wistar-Imamichi male rats (200 g) was cut with a hair clipper or a shaver under anesthesia with ether and the preparation was applied to the abdominals skin (3 x 3 cm). Eight hours after application of the preparation, the rats were sacrificed and the stratum corneum was removed thoroughly, by stripping with cellophane adhesive tape on the skin at the middle of the part where the preparation was applied. After removing fat, capillary vessels, and the like in dermis, a part of the dermis was taken out by punching with a puncher(ϕ 1.0 cm) and cut into thin strips. Then, the thin strips of the skin section were mixed with 2 ml of methanol, 1 ml of an ethanol solution of ethyl p-hydroxybenzoate (internal standard substance) (10 μ g/ml), and 0.5 ml of 50 mM ammonium acetate buffer (pH 6.0). The resulting mixture was homogenized well by microhomogenization and centrifuged at 15,000 rpm for 5 min. The resulting supernatant was applied to HPLC. The same conditions for HPLC as in Test Example 1 were followed.

Table 2

Effect of skin absorption aid on transdermal absorption of tranilast		
Absorption aid	Penetration rate (μ g/cm^2/h)	Drug concentration in skin (μ g/g)
-	0.22 ± 0.01	26.01 ± 1.29
2% propylene glycol	0.38 ± 0.07	44.93 ± 4.66
5% propylene glycol	0.33 ± 0.07	45.92 ± 8.71
10% propylene glycol	0.68 ± 0.10	35.24 ± 0.69
2% butanediol	0.50 ± 0.13	36.04 ± 5.08
5% butanediol	0.64 ± 0.18	49.74 ± 7.19
10% butanediol	0.83 ± 0.07	33.08 ± 0.92
2.5% N-methyl-2-pyrrolidone	0.68 ± 0.10	53.23 ± 10.88

Claims

1. A preparation for external application containing an aqueous base comprising tranilast, its salt, or a mixture thereof

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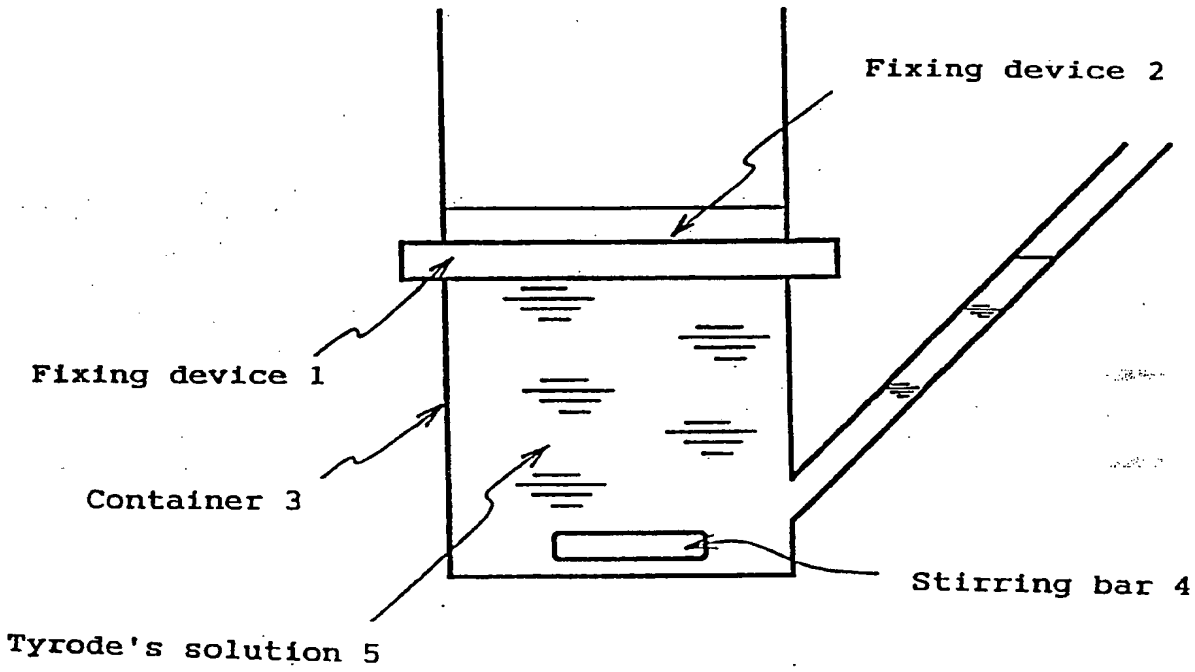

Fig. 1

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/00283

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 2-264716, A (Kissei Pharmaceutical Co., Ltd.), October 29, 1990 (29. 10. 90) & EP, 391002, A1 & US, 5356620, A	1 - 13
A	JP, 1-294620, A (Kissei Pharmaceutical Co., Ltd.), November 28, 1989 (28. 11. 89) (Family: none) & Chem. abst., Vol. 112, No. 204742	1 - 13
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P,A	JP, 9-12488, A (Read Chemical K.K.), January 14, 1997 (14. 01. 97) & EP, 751107, A1	1 - 13

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